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EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,541	BRODSKY, GARY	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *9-13,17-37 and 41-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 14-16, and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050808*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-8, in the reply filed on July 28, 2005 is acknowledged. The traversal is on the ground(s) that a search of compositions of Groups I, IV, V, and XII and the method claims of Groups VII, VIII, XIV, and XV would not be an undue burden. Applicants state that Group IV drawn to a protein comprising SEQ ID NO: 4, and variants thereof would be sufficient to examine the subject matter of Groups I, IV, V, and XII. Applicants state that a thorough search for the subject matter of the product groups will be sufficient to examine the claims of the method groups. This is found persuasive for the product claims, therefore Groups I, IV, V, and XII (claims 1-8, 14-16, and 38-40) will be rejoined and are currently being examined. The product claims are distinct from the method claims because the product can be used in a materially different method as stated in the restriction requirement (see page 7 of Restriction requirement mailed 6/29/2005). Therefore, it would be an undue burden to search the distinct inventions of Groups VII, VIII, XIV, and XV together.

2. Claims 9-13, 17-37, and 41-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 28, 2005.

The requirement is made FINAL.

Priority

3. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e). The priority date is March 18, 2003.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on August 8, 2005 is being considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities:

6. On page 11, the Brief Description of the Figures of the Inventions for Figure 1 does not match the drawings, which disclose digital images of Western blots for prelamin-GFP fusion proteins using anti-GFP antibody (Figures 1A), and anti-prelamin A antibody (Figure 1B).

7. On page 79, line 18, the beginning of the sentence is not capitalized. Suggest, "~~prelamin~~ ~~A~~ Prelamin A was detected...".

Appropriate correction is required.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

9. Claims 39 and 40 are objected to because of the following informalities:

10. In claim 39, the identification of amino acids is not uniform in the claim. Suggest identifying all amino acids with three letter abbreviations.

11. In claim 40, there is a typographical error. The Asparagine at position 195 in SEQ ID NO: 4 is identified as position 19. Suggest, "...~~Asn19Lys~~ Asn195Lys, and Arg377His."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-8, 14-16, and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a composition comprising SEQ ID NO: 4 that affects the formation of normal nuclear lamina structures, and the differentiation of cardiac and skeletal myoblast, does not reasonably provide enablement for isolated complexes comprising **fragments, peptides that differ by at least one substitution, deletion, or insertion, and peptides that are at least 70% identical of SEQ ID NO: 2, and SEQ ID NO: 4** that would affect the formation of normal nuclear lamina structures, and induction of myoblast activation and differentiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn a therapeutic composition comprising a pharmaceutically acceptable carrier, a therapeutic protein comprising a protein that is at least 70% identical to SEQ ID NO: 4, wherein the protein has prelamin A or lamin A biological activity, wherein the protein is chemically or recombinantly attached to a therapeutic agent that increases the half-life of the protein in cardiac or skeletal muscle tissue; a therapeutic composition for promoting myoblast activation and growth or regeneration of cardiac or skeletal

muscle comprising an isolated fragment of SEQ ID NO: 4 with inter-nuclear transport domain biological activity, or a biologically active homologue thereof, and a processing deficient prelamin A peptide that consists essentially of an amino acid sequence that differs from SEQ ID NO: 4 by at least one substitution, deletion, or insertion.

The peptides encompassed to be therapeutic proteins include isolated peptides selected from the group consisting of a peptide consisting essentially of SEQ ID NO: 2 and SEQ ID NO: 4, a biologically active fragment of SEQ ID NO: 2 and SEQ ID NO: 4, a peptide consisting essentially of an amino acid sequence that is at least 70 % identical to SEQ ID NO: 2, wherein the peptide has the biological activity of SEQ ID NO: 2, respectively, a peptide consisting essentially of an amino acid sequence that differs from SEQ ID NO: 2 by at least one substitution, deletion or insertion of an amino acid residue at a position of SEQ ID NO: 2 selected from the group consisting of: 1, 2, 5, 6, 9, 10, 11, 12, 13, and 14, wherein the peptide has the biological activity of SEQ ID NO: 2, a SEQ ID NO: 2 peptide disclosed above with a modification selected from a group consisting of farnesylation, carboxymethylation, geranylgeranylation, and complexing with a lipid carrier.

2.) The breadth of the claims: the claims are extremely broad in that a very large number of constituents could be encompassed by peptide **fragments and homologues thereof** of proteins selected from the group of proteins recited that would be considered to be useful as a therapeutic compositions for promoting myoblast activation and growth or regeneration of cardiac or skeletal muscle.

3.) The predictability or unpredictability of the art: / 7.) The state of the prior art: the prior art has shown that "nuclear lamina maintains nuclear shape and volume, and may also be

involved in the organization of chromatin in the interphase nucleus. In most mammalian cells, the nuclear lamina consists of three class V intermediate filament proteins, lamins A, B, C. Prelamin A is the precursor of nuclear lamin A protein. It possesses a CAAX box, and has been shown to be farnesylated in vitro. Experiments have shown that nonprenylated CAAX box mutants of prelamin A enter the nucleus, yet are not proteolytically processed and are not incorporated into the nuclear lamina." (see Kilic, F. et al. 2nd paragraph of Introduction). There is predictability in the art for the requirement of a requisite tertiary structure during the interaction of a substrate with its cognate enzyme. Park, H-W. et al. state the affinity of a protein substrate for farnesyltransferase is affected by basic amino acid residues upstream of the CAAX motif, which encompass amino acids disclosed by SEQ ID NO: 2 and SEQ ID NO: 4 (see Park, H-W. et al. Science 275: 1800-1804 (1997), page 1804, 1st column, 3rd indented paragraph). Thus the art has shown that protein farnesyltransferase and geranylgeranyltransferase enzymes have binding sites that require distinct tertiary structure for proper enzyme-substrate binding and subsequent farnesylation/geranylgeranlylation of the peptide substrate by the enzyme. Thus, there is no way to predict whether any of the **fragments or homologues** will interact with farnesyltransferase and geranylgeranyltransferase enzymes.

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the specification provides guidance with respect to the site-directed mutagenesis of Arg 60 Gly, Leu 85 Arg, Arg 89 Leu, Asn 195 Lys, Glu 203 Gly, and Arg 377 His amino acids(with respect to SEQ ID NO: 4) affect on myotube formation discussed in the working examples (Example 3), but provides no guidance whatsoever in selecting which fragments and homologues might affect nuclear lamina function on developing myotubes.

Further, no guidance is provided as to how to determine which fragments and homologues might work.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which fragments and homologues, are capable of regulating nuclear lamina formation during the process of myoblast activation.

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

14. Claims 1-5, 7, 8, 14-16, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to biologically active fragments of SEQ ID NO: 2 and SEQ ID NO: 4; a peptide consisting of an amino acid sequence that is at least 70% identical to SEQ ID NO: 2 and SEQ ID NO: 4, wherein the peptide has the biological activity of SEQ ID NO: 2 and SEQ ID NO: 4, respectively; a peptide consisting essentially of an amino acid sequence that differs from SEQ ID NO: 2 by at least one substitution, deletion, or insertion of an amino acid residue at a

position selected from the group consisting of 1, 2, 5, 6, 9, 10, 11, 12, 13, and 14, wherein the peptide has the biological activity of SEQ ID NO: 2; and a processing deficient prelamin A peptide consisting essentially of an amino acid sequence that differs from SEQ ID NO: 4 by at least one substitution, deletion or insertion that results in a decrease in a prelamin A or prelamin A propeptide biological activity . SEQ ID NO: 4 encodes human prelamin A protein. SEQ ID NO: 2 corresponds to amino acid residues 647 to 661 of prelamin A, wherein the cysteinyl at position 661 is farneylated during lamin A maturation. To satisfy the written description requirement, the specification must describe the invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

The specification does not describe the structure, that is amino acids in the various polypeptides that can be altered without affecting the function of a specific polypeptide. For one to be in possession of the claimed invention, the inventor would have to know the functional consequences of structural alterations to SEQ ID NO: 2 and SEQ ID NO: 4. Claims 1(d), 4, and 5, 14-16, and 38-40 encompass peptides that would have more than one deletion, including deletions at all positions enumerated. The disclosure of the application does not describe biologically active deletion peptides of SEQ ID NO: 2. Applicants disclosure at paragraph [0096] state the inventors envision making amino acid substitutions to amino acid residues corresponding to amino acids in SEQ ID NO: 2, based on the alignment of other prelamin A sequences from other species. The disclosure does not describe the effects of altered peptide substrates (SEQ ID NO: 2 modified peptides) on enzyme-substrate association. Park, H-W. et al. state the affinity of a protein substrate for farnesyltransferase is affected by basic amino acid residues upstream of the CAAX motif, which encompass amino acids disclosed by SEQ ID NO:

2 (see Park, H-W. et al. Science 275: 1800-1804 (1997), page 1804, 1st column, 3rd indented paragraph). Thus the art has shown that protein farnesyltransferase and geranylgeranyltransferase enzymes have binding sites that require distinct tertiary structure for proper enzyme-substrate binding and subsequent farnesylation/geranylgeranlylation of the peptide substrate by the transferase enzyme. Therefore, due to the limited predictability in the art, a skilled artisan would not find adequate support for all the peptides as disclosed in the claims.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Kilic, F. et al. (Journal of Biological Chemistry, 272(8): 5298-5304 (1997)).

Kilic, F. et al. disclose the solid phase synthesis of a peptide that has the sequence, H_2N-RSYLLGNSSPRTQSPQNC-OCH_3 (see Experimental Procedures, page 5299, Peptide Synthesis section). The isolated peptide consists essentially of SEQ ID NO: 2. The peptide has 100% identity with SEQ ID NO: 2, with the insertion of three amino acids, RSY, at the amino terminus. The prelamin A peptide is farnesylated and geranylgeranylated (see Experimental Procedures, page 5299, 2nd and 3rd paragraph of Peptide Synthesis section, and Figure 2, current application, claims 1-8).

17. Claims 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Fatkin, D. et al. (IDS document # 6). Fatkin, D. et al. disclose 4 processing deficient prelamin A peptides, wherein the processing deficient prelamin A peptide consists of an amino acid sequence that differs from SEQ ID NO: 4 by a substitution of an amino acid in SEQ ID NO: 4. The disclosed amino acid sequences have the following substitutions, Arg 60 Gly, Leu 85 Arg, Asn 195 Lys, and Glu 203 Gly (see pages 1718-1719, Results Genetic studies section, and Figure 2B, current application, claims 38-40).

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 12, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER